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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,718	01/03/2002	David S. Hungerford	21418-PA-DIV	4599

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,718	HUNGERFORD ET AL	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-46 and 58-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-46 and 58-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment of 1/26/05 canceled claims 1-35, 47-57 and 71-83, and amended claims 36, 37, 43, 58-60, 64 and 67.

Claims examined on the merits are 36-46 and 58-70, which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claims 40, 41 and 65 are objected to because of the following informalities: in line 2 of claim 40, "spin-culture" should be changed to --- spinner culture --- to be consistent with the amendment to claim 36 reciting "spinner culture". In line 1 of claims 41 and 65, "low" should be changed to --- reduced --- to be consistent with "reduced" recited in claim 40 on which claim 41 depends and recited in claim 64 on which claim 65 depends.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Obtaining a healthy chondrocyte specimen for "non-diseased or injured part" of a patient's body as required in line 3 of claim 36 is not found in the specification. The page and line where "non-diseased or injured part" is recited as to where the healthy specimen is obtained should be pointed out.

Claim Rejections - 35 USC § 103

Claims 36-39, 42-46, 58-63 and 66-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glorioso et al (6,413,511 B1) in view of Frondoza et al and Schinstine et al (5,858,747) and Cherksey (6,264,943 B1), and if necessary in further view of Armstrong (5,830,507) for reasons in the previous office action of 10/29/04 and for reasons herein.

The claims are drawn to a method of repairing diseased or injured tissue by surgically obtaining healthy tissue or a healthy chondrocyte specimen from a different part of a patient's body, rapidly growing cells from the tissue or chondrocytes externally of the patient's body by spinner culture on microcarrier particles, and surgically implanting the grown cells or the grown chondrocytes into the diseased or injured tissue of the patient.

Glorioso et al disclose (col 6, lines 31-45 and col 28, lines 20-25) transplanting transfected chondrocytes to repair a defect such as an articular cartilage defect (col 15, lines 62-67). Autologous

chondrocytes are retrieved for *in vitro* culture (col 45, lines 30-35) prior to transfection and transplantation (col 29, lines 5-12).

Frondoza et al disclose culturing of chondrocytes on microcarriers in a spinner flask (page 881, left col). Microcarriers used include dextran beads, collagen-coated dextran beads, crosslinked dextran containing N,N,N-trimethyl-2-hydroxyaminopropyl groups and crosslinked dextran containing covalently bound type I collagen (page 880, right col). Microcarrier suspension culture supported growth and enhanced expression of the chondrocytic phenotype (abstract, page 879).

Schinstine et al disclose (col 3, lines 17-45) that when cells do not have a substrate available in a bioartificial organ (BAO), the cells tend to adhere to each other and form dense agglomerations or aggregates that can develop necrotic regions due to relative inaccessibility of nutrients and oxygen. Microcarriers can provide a growth surface in the BAO (col 17, lines 24-54). The microcarriers can allow a greater number of cells to be encapsulated and evenly distributed within the BAO. The microcarrier can be a Cytodex dextran microcarrier or be collagen or EMC coated microcarriers (col 17, lines 29-39).

Cherksey discloses (col 5, lines 9-18) that culturing cells *in vitro* on a support matrix such as glass beads before the cells are transplanted into a mammalian brain results in prolonged survival and viability *in vivo*.

Armstrong discloses (col 3, lines 46-54), in reference to the prior art, that it is known to attach hepatocytes to collagen-coated cross-linked dextran microcarriers, and implant the microcarriers in the peritoneal cavity of rats. The microcarriers provide a surface of attachment so the hepatocytes survive and function *in vivo*. The microcarriers do not degrade once implanted. Armstrong further discloses, in regard to the invention, culturing cells with microcarriers such as cross-linked dextran to provide cell-coated microcarriers, and using the cell-coated microcarriers to repair a skin injury (col 5, line 6 to col 7, line 7). The cell-coated microcarriers can be harvested, concentrated and put into maintenance medium for shipment to a remote treatment center (col 14, lines 41-52). Due to a uniform suspension of microcarriers, each microcarrier has a similar number of attached cells resulting in a homogeneous population for subsequent application on a skin injury (col 7, lines 35-42).

When culturing chondrocytes for implanting as disclosed by Glorioso et al, it would have been obvious to culture the chondrocytes on a microcarrier in a spinner flask as suggested by Frondoza et al disclosing this method of culturing as supporting chondrocyte growth and enhancing phenotye, and as further suggested by Schinstine et al disclosing culturing cells on microcarriers to prevent the formation of necrotic regions and as also suggested by Cherksey disclosing that culturing cells on glass beads before transplanting into the mammalian brain results in prolonged survival and viability *in vivo*. Obtaining

cells from a different part of the body would have been obvious to not further damage an injury being repaired and Glorbioso et al discloses using autologous cells. If needed, Armstrong would have further suggested the invention from a disclosure of culturing cells on microcarriers before implanting. The conditions of dependent claims would have obvious matters of choice depending on individual preference in view of conditions disclosed by the references. Selecting a specific region of the body to obtain the cells and to implant the cells would have been a matter of individual preference depending on the tissue defect to be repaired. In regard to claims directed to a crosslinked polysaccharide, Frondoza et al disclose crosslinked dextran containing covalently bound type I collagen, and a polysaccharide crosslinked with a polyamine such as dextran crosslinked with gelatin would have been obvious therefrom.

Response to Arguments

Applicant's arguments filed 1/26/05 have been fully considered but they are not persuasive.

Applicants urge that Frondoza et al cannot be combined with Glorioso et al since Glorioso et al employ transfected cells and Frondoza et al employ unaltered chondrocytes. However, the cells of Glorioso et al being transfected would not have led one to believe that a spinner flask will not function to support chondrocyte growth and enhance phenotype as disclosed by Frondoza et al. The chondrocytes of Glorioso et al are transfected to express a protein,

and expressing this protein will not be expected to change the behavior of the chondrocytes in a spinner flask.

While cells disclosed by Schinstine et al and Cherksey may not be chondrocytes as urged by applicants, these references are combined with the Frondoza et al reference, which discloses culturing chondrocytes on microcarriers. The references are combined together and must be considered in combination as a whole. When Frondoza et al is considered, it would have been obvious that chondrocytes can be grown on a microcarrier. There is seen no reasons why culturing chondrocytes on a microcarrier as disclosed by Frondoza et al will not prevent the formation of necrotic regions as disclosed by Schinstine et al and provide prolonged survival and viability *in vivo* as disclosed by Cherksey when culturing cells other than chondrocytes. These type of comments also apply to Armstrong culturing cells that are not chondrocytes.

Applicants urge that dependent claims 37, 44, 46, 59 and 68-70 are unobvious. However, obtaining healthy chondrocytes from nasal sptal cartilage as in claim 37 would have been obvious when this is the type of cartilage being repaired. Obviously one is going to repair tissue with the type of cells that form the tissue, and not with cells that form some other tissue. As to claims 44, 46 and 68-70, the cross-linking conditions required are obvious for reasons set forth at page 10, lines 14-20, of the previous office action. A source of a healthy tissue specimen such as cartilage as required by claim 59 would have been obvious when cartilage is the tissue being

repaired. As noted above, one is not going to repair tissue with cells that do not form the tissue.

Claim Rejections - 35 USC § 103

Claims 40, 41, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 36-39, 42-46, 58-63 and 66-70 above, and further in view of Starling et al (4,839,215).

The claims require culturing the cells in a reduced or low oxygen environment.

Starling et al disclose culturing chondrocytes (col 18, line 62) in a carbon dioxide incubator (col 19, lines 1-5). The cells maintained their phenotype and increased in number over hundred fold.

When culturing the chondroctyes of Glorioso et al on a microcarrier and in a spinner flask as set forth above, it would have been obvious to culture in a carbon dioxide atmosphere as suggested by Starling et al disclosing culturing chondrocytes in a carbon dioxide incubator where phenotype is maintained and the number of cells is increased over a hundred fold. Maintaining phenotype and increasing cell number over a hundred would have been expected to be an advantage. The carbon dioxide atmosphere would have provided a reduced oxygen content as claimed.

Response to Arguments

Applicants urge that Starling et al do not disclose spinner culture. However, the use of spinner culture is suggested by references applied above, and Starling et al is not relied on for

suggesting spinner culture. The affect of a carbon dioxide atmosphere disclosed by Starling et al would have been expected to occur when using spinner culture as when not using spinner culture. Starling et al do not disclose that the result of an atmosphere of carbon dioxide depends on culturing in a Petri dish. As to about 5% of oxygen required in claims 41 and 65, this amount of oxygen will inherently result when providing a carbon dioxide atmosphere as suggested by Starling et al.

Double Patenting

Claims 36-39, 42-46, 58-63 and 66-70 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,378,427 B1 or claims 1-9 of U.S. Patent No. 6,662,805 B2 in view of Frondoza et al.

The claimed invention and Frondoza et al are described above.

The claims of the patents require a method substantially as presently claimed except for culturing the chondrocytes on a microcarrier using spin-culture.

It would have been obvious to culture the chondrocytes of the claims of the patents with a microcarrier using a spinning flask as disclosed by Frondoza et al when culturing chondrocytes since this culturing method is suggested by Frondoza et al as an advantageous method for culturing chondrocytes.

It does not appear the present claims are non-elected claims resulting from a restriction requirement as compared to the claims of the patents.

Double Patenting

Claims 40, 41, 64 and 65 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,378,427 B1 or claims 1-9 of U.S. Patent No. 6,662,805 B2 in view of Frondoza et al as set for above, and in further view of Starling et al.

The invention and Starling et al are described above.

When using a microcarrier and spinning flask in the methods of the claims of the patents claims as set forth above, it would have been obvious to culture in a carbon dioxide atmosphere as suggested by Starling et al disclosing culturing chondrocytes in a carbon dioxide incubator where phenotype is maintained and the number of cells is increased over a hundred fold. Maintaining phenotype and increasing cell number over a hundred would have been expected to be an advantage. The carbon dioxide atmosphere would have maintained a reduced oxygen content as claimed.

Double Patenting

Claims 36-46 and 58-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No. 10/654,057 or claims 1-35 of copending Application No. 10/066,992. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention of using spin-culture to culture cells on microcarriers to repair defective tissue would have been obvious from the claims of the

copending applications that contain claims requiring culturing chondrocytes on microcarriers using spin-culture conditions and a low oxygen environment to produce chondrocytes for implanting.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting

Claims 36-39, 42-46, 58-63 and 66-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of copending Application No. 09/825,632. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention would have been obvious from claims of the copending application including claims drawn to culturing chondrocytes on a microcarrier for implanting and claims that require a spinner culture apparatus for culturing.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting

Claims 40, 41, 64 and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of copending Application No. 09/825,632 as set forth above, and further in view of Starling et al who would have suggested a low oxygen environment when culturing for reasons set forth above when applying Starling et al.

Response to Arguments

The above double patenting rejections have not been traversed.

Conclusion

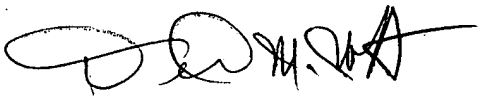
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 751-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David M. Naff
Primary Examiner
Art Unit 1651

DMN
4/29/05